بسم الله الرحمن الرحيم

University of Khartoum
Graduate College
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Prevalence Bleeding Disorders among Women Presenting with Menorrhagia in Khartoum Teaching Hospital

By

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M.B.B.S (University of Khartoum, 1999)

A thesis submitted in partial fulfillment for the requirements of the Degree of MD in Clinical Pathology, 2009

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Dedication

To

my

family

the people whom I love, respect and appreciate

Acknowledgements

All praise and thanks to Allah, who blessed me, by putting all those wonderful people on my way, for preparation and completion of this study.

With a great deal of respect I want to thank my supervisor Dr. Maria Mohamed Hamad Satti, who spared neither time nor effort in enlightening and helping me.

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It is a pleasure to express my respect and sincere thanks to all of my colleagues and my friends for their help and support.

I want to extend my deep thanks to all test subjects for agreement to participate in this study.

I am privileged by a very marvelous and wonderful family, to whom I would like to express my gratitude for their patience, courage, support and inspiration.

Abstract

Introduction:

Menorrhagia is a common problem among females. It has many causes. It is common among patients with bleeding disorders and can be a presenting symptom.

Objectives:

To assess the prevalence of bleeding disorders among women with menorrhagia

Study design and procedure:

This is a cross-sectional descriptive study, coducted in Khartoum Hospital (Dec2007-Feb2008); 34 women aged between 13 and 43 years presenting with menorrhagia were studied, where the usual gynecological and endocrinal causes of bleeding were ruled out by a gynaecologist. These patients were investigated for haemostatic defects by doing; platelet count and finger prick platelet aggregation test, bleeding time, prothrombin time, activated partial thromboplastin time, and when appropriate thrombin time and factor assay and factor XIII screening. Factor VIII level, vWf antigen, were done for all patients.

Results and discussion:

Of the 34 women investigated, 56% (19 cases) had a bleeding disorder to account for their menorrhagia. Although a majority of patients with platelet disorders and von Willebrand's disease (vWd), (47%) and (32%) respectively, other rare coagulation factor deficiencies such as factor V (10.5%), and factor X (10.5%) were also found. Platelet disorders included count and function defects. History of bleeding from other sites, appeared as a significant finding, which might be used as a predictor for such a disorder in patients with menorrhagia. Family history of bleeding tendencies was not a predictive finding.

Conclusion and recommendations:

Patients with menorrhagia without a discernable cause, therefore, need evaluation for haemostatic disorders. This necessitate collaborate work between gynaecologists and haematologists, to exclude haemostatic abnormality. Especially before surgical intervention. vWd needs special consideration, since it might be missed by routine investigations. There should be a reliable, specialized laboratory in coagulation to reduce the discrepancy of results.

مستخلص

مقدمة:

زيادة الطمث مشكلة كثيرة الحدوث لدى النساء،وهنالك اسباب عديدة لحدوثه.وهو ايضا عرض لكثيرالحدوث لدي مريضات عدم تجلط الدم.

الاهداف:

تقدير نسبة وجود مشاكل عدم تجلط الدم لدى النساء اللاتي يعانين من زيادة في كميـة الطمث.

منهجية البحث:

هذه دراسة مقطعية وصـفية اجريـت فـي مستشـفى الخرطـوم(ديسـمبر2007-فبراير2008). تضمنت الدراسة 34 امرأة تتراوح اعمارهن 13-43 وتـم تشـخيص حالتهن بواسطة طبيب نساء وتوليد لاستبعاد اسباب موضعية لاعراضهن المرضية. تم اجراء الفحوصات اللازمة لتقصي سبب زيادة النزف لديهن.وتضمن ذلك فحص لعـدد الصفائح الدموية ووظيفتها،فحوصات اولية لعوامل التجلط، وفحوصات لمعرفة العامـل الناقص في حالة وجود خلل.

نتائج الدراسة :

وجد ان 56% منهن تعاني خلل في تجلط الدم. اغلبها 47%مشـاكل فـي الصـفائح الدموية و32%نقص في عامل التجلط vWf ، نقص كل من العـاملين VوX بنسـبة 10,5%لكل منهما. وجود اعراض اخرى لزيادة النزف كانـت ملاحظـة ذات دلالـة احصائيةلدى النساء محور الدراسة. ولكن تاريخ الاسرة لم يكن علامة مهمـة لوجـود

خلل في تجلط الدم لديهن.

الخلاصة والتوصيات:

وتم التوصية باعتبار عدم تجلط الدم سبب محتمل لدي النساء اللاتي يعانين من زيـادة الطمث. ويجب اجراء الفحوصات اللازمة لتشخيص الحالة،وخصوصـا فـي حـالات التدخل الجراحي والتعاون وتبـادل الاستشـارة بـين اختصاصـي النسـاء والتوليـد واختصاصي أمراض الدم.عامل التجلط vWf يجب اعتباره بصورة خاصة، حيـث ان الفحوصات الاولية غير قادرة دائما على الكشف عنه. و يجب وجود معمل متخصـص في مجال التجلط لتقليل نسبة الخطأ في تشخيص مثل هذه الحالات.

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List of Abbreviations

ACOG: American college of obstetrics and gynaecology.

ADP : Adenosine 5'-diphosphate.

aPTT: Activated partial thromboplastin time.

Ca^2 : Calcium.

CDC : Centers for Disease Control and Prevention.

COC : Combined oral contraceptives.

DDAVP: Desmopressin.

DIC : Diffuse intravascular coagulation.

DUB : Dysfunctional uterine bleeding .

EDTA: Ethylenediamine tetracitic acid (anticoagulant).

ELISA: Enzyme-linked immunosorbent techniques.

FDPs : Fibrin(ogen) degradation products.

GI : Gastrointestinal.

HTCs: Hemophilia treatment centers.

INR : International Normalization Ratio.

IUD: Intra Uterine Contraceptive Device.

LNG-IUS: Levonorgestrel intrauterine system.

M : Molar.

Min: Minute.

MW : Molecular weight.

NHLBI: National Heart and Lung and Blood Institute.

NSAID: Non steroidal anti inflammatory drugs.

PCOS : Polycystic ovary syndrome.

PH: Minus logarithm the Hydrogen concentration.

PL: Phospholipids.

ppp : Platelet poor plasma.

PT: Prothrombin time.

Ref. : reference.

Sec : Seconds.

TF : Tissue factor.

TMB : Tetra methyl benzidine.

TT : Thrombin time.

UK: United Kingdom.

US : United States of America.

VIIa: Activated coagulation factor seven.

vWD : von Willebrand disease.

vWf : von Willebrand factor.

w/v: Weight per volume.

Xase : Enzyme cleavage of factor ten (X).

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Chapter One

1. INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION:

Menstruation is the monthly process by which the endometrium in fertile women is discarded if no pregnancy occurs. (1)

A normal menstrual cycle is 21-35 days in duration, with bleeding lasting an average of 5 days and total blood flow between 25 and 80 ml. A blood loss of greater than 80 ml or lasting longer than 7 days constitutes menorrhagia (also called hypermenorrhea). In practice this is not usually directly measured by patients or doctors. Menorrhagia also occurs at predictable and normal (usually about 28 days) intervals, distinguishing it from menometrorrhagia, which occurs at irregular and more frequent intervals. It is possible to estimate the amount of bleeding by the number of tampons or pads a woman uses during her period. As a guide a regular tampon fully soaked will hold about 5ml of blood.(2)

Menorrhagia is a very common complaint, affecting about 1 in 5 of all women of reproductive age. In the United Kingdom, for example, it accounts for about 12% of all patients referred to gynecologists.(3) Some people report its frequency as 30% of women in reproductive age. Recently, underlying bleeding disorders, particularly von willebrand's disease and platelet dysfunction, have been found to be prevalent in women with menorrhagia.(3,4) The condition should always be diagnosed by a doctor to rule out a variety of potentially serious underlying conditions such as cancer and uterine fibroids.(5)

Menorrhagia is a common symptom in patients with bleeding disorders. Studies have documented increased morbidity due to excessive bleeding in girls

and women. Women with bleeding disorders are more likely to be iron deficient and to have received blood transfusions. They are also more likely to undergo gynecologic surgical procedures and to have bleeding complications related to those and other surgical procedures. Furthermore, a number of studies have shown the effect of this excessive bleeding, particularly menorrhagia, on quality of life, including increased symptoms of depression, and increased days lost from work and social activity. Since menorrhagia in women with bleeding disorders frequently begins at menarche, these factors could have an impact on the social and academic development of the adolescent female.[3,6]

1 -2- Literature review:

1-2-1- Defining the Problem:

Menstrual problems may relate to the regularity, frequency or even the character of bleeding, but most commonly it is heavy periods, menorrhagia, which lead to a request for medical help. The problem of providing adequate health care for women with menorrhagia is immense as many women perceive their periods to be heavy, although, only some of them ever seek medical advice. Furthermore, even when a woman presents with the complaint of menorrhagia, the methods used to decide whether or not she has a clinical problem requiring treatment and any subsequent treatment options offered to her will be related to what is available from her healthcare provider and the availability of medical care as a fee-paying or government-provided service. Hence the management of menorrhagia varies enormously between cultures and between countries.[5]

1-2-2 Pathophysiology of menorrhagia:

Knowledge of normal menstrual function is imperative in understanding the etiologies of menorrhagia. Four phases constitute the menstrual cycle, follicular, luteal, implantation, and menstrual. In response to gonadotrophin-releasing hormone (GnRH) from the hypothalamus, the pituitary gland synthesizes follicle stimulating hormone (FSH) and luteinizing hormone (LH), which induce the ovaries to produce estrogen and progesterone. During the follicular phase, estrogen stimulation results in an increase in endometrial thickness. This also is known as the proliferative phase. The luteal phase is intricately involved in the process of ovulation. During this phase, also known as the secretory phase, progesterone causes endometrial maturation. If fertilization occurs, the implantation phase is maintained. Without fertilization, estrogen and

progesterone withdrawal results in menstruation.[7] Without ovulation, the corpus luteum fails to form, resulting in no progesterone secretion. Unopposed estrogen allows the endometrium to proliferate and thicken. The endometrium finally outgrows its blood supply and degenerates. The end result is asynchronous breakdown of the endometrial lining at different levels. This also is why anovulatory bleeding is heavier than normal menstrual flow.[7]

The physiology and pathology of menstruation has been extensively studied; still several steps are not fully understood. A study supports a chain of events linking progesterone withdrawal to upregulation of the thrombin receptor, leading to an increased thrombin response and a release of edothelin, in turn leading to constriction in the coiled arteries. Thrombi are seen in the functional layers but are limited to the shedding surface of the tissue. These thrombi are known as "plugs" because blood can only partially flow past them. Fibrinolysis limits the fibrin deposits in the unshed layer. Following thrombin plug formation, vasoconstriction occurs and contributes to hemostasis. The results also show that there is a high probability of revealing an earlier undiagnosed bleeding disorder when properly examining a woman with menorrhagia. Furthermore there was a significant correlation between the amount of menstrual blood loss and the fibrinolytic activity in the menstrual fluid both for women who bleed normally and for women with menorrhagia.[1]

1-2-3- Causes of Menorrhagia:

Etiologies of menorrhagia are divided into 4 categories: organic, endocrinologic, anatomic, and iatrogenic.

1-2-3-1 Organic causes of menorrhagia: include infection, bleeding disorders, and organ dysfunction.

- Infections can be of any genitourinary origin, sexually transmitted diseases are of greater concern.

- Coagulation disorders can manifest as heavy menstrual bleeding, these include von Willebrand disease; coagulation factors deficiency; idiopathic thrombocytopenic purpura (ITP); and platelet dysfunction. [7] Hemostasis of the endometrium is directly related to the functions of platelets and fibrin. Deficiencies in either of these components results in menorrhagia.[1]
- Organ dysfunction causing menorrhagia includes hepatic or renal failure. Chronic liver disease impairs production of clotting factors and reduces hormone metabolism (e.g., estrogen). Either of these problems may lead to heavy uterine bleeding. In patients with renal failure, gonadal resistance to hormones and hypothalamic-pituitary axis disturbances result in menstrual irregularities. Most women in this renal state are amenorrhoeic, but others also develop menorrhagia. If uremic coagulopathy ensues, it usually is due to platelet dysfunction and abnormal factor VIII function. The resulting prolonged bleeding time causes menorrhagia that can be very tenuous to treat.[7]

1-2-3-2 Endocrine causes of menorrhagia: include thyroid and adrenal gland dysfunction, pituitary tumors, anovulatory cycles, polycystic ovary syndrome (PCOS), obesity, and vasculature imbalance.

- Both hypothyroidism and hyperthyroidism result in menorrhagia. Even subclinical cases of hypothyroidism produce heavy uterine bleeding in 20% of patients. Menorrhagia usually resolves with correction of the thyroid disorder.
- Prolactin-producing pituitary tumors cause menorrhagia by disrupting (GnRH) secretion. This leads to decreased LH and FSH levels, which ultimately cause hypogonadism. Interim stages of menorrhagia result until hypogonadism manifests.
- The most common etiology of heavy uterine bleeding is anovulatory cycles. The finding of menorrhagia at irregular intervals without any

known organic etiology confirms the clinical diagnosis. This is most common in adolescent and perimenopausal populations.

- The hallmarks of PCOS are anovulation, irregular menses, obesity, and hirsutism. Insulin resistance is common and increases androgen production by the ovaries.
- Hyperinsulinemia is a direct consequence of obesity. This overproduction of insulin leads to ovarian production of androgens, as occurs in PCOS.
- Vasculature imbalance is theorized to be the result of a discrepancy between the vasoconstricting and aggregating actions of prostaglandin F2 (alpha) and thromboxane A2 and the vasodilating actions of prostaglandin E2 and prostacyclin on the myometrial and endometrial vasculature.(7)

1-2-3-3 Anatomic etiologies for menorrhagia: include uterine fibroids, endometrial polyps, endometrial hyperplasia, and pregnancy.

Fibroids and polyps are benign structures that distort the uterine wall and/or endometrium. Either may be located within the uterine lining, but fibroids may occur almost anywhere on the uterus.

Endometrial hyperplasia usually results from unopposed estrogen production, regardless of the etiology. Endometrial hyperplasia can lead to endometrial cancer in 1 -2% of patients with anovulatory bleeding, but it is a diagnosis of exclusion in postmenopausal bleeding.

Anatomic defects or growths within the uterus can alter either of the aforementioned pathways (endocrinologic/haemostatic), causing significant uterine bleeding. The clinical presentation is dependent on the location and size of the gynecologic lesion. (7)

1-2-3-4 latrogenic causes of menorrhagia: include (intra uterine contraceptive device) IUDs, steroid hormones, chemotherapy agents, and medications (e.g. anticoagulants).

- IUDs can cause increased menstrual bleeding and cramping due to local irritation effects.
- Steroid hormones and chemotherapy agents disrupt the normal menstrual cycle, which is restored easily upon cessation of the products.
- Anticoagulants decrease clotting factors needed to cease any abnormal blood flow, including menses. This type of menorrhagia also is easily reversible.

Etiologic causes are numerous and often unknown. If the bleeding workup does not provide any clues to the etiology of the menorrhagia, a patient often is given the diagnosis of dysfunctional uterine bleeding (DUB). Most cases of DUB are secondary to anovulation. [7]

Due to the overwhelming factors that can contribute to the dysfunction of either the endocrine or haematological pathways, in depth knowledge of an existing organic disease is just as imperative as understanding the menstrual cycle itself.[1,7]

1-2-4- Diagnosis of Menorrhagia:

The definition and diagnosis of heavy menstrual bleeding in women is tricky, because how one defines "heavy bleeding" is such a relative concept. Both the women's perception and the physician's perception of the importance of heavy menstrual-bleeding come into play. Since bleeding disorders tend to run in families, having a heavy menstrual flow may be considered normal in that family.[8]

1-2-4-1- Measurement of menstrual loss

One of the major problems confronting all clinicians is how to quantify the amount of menstrual loss which a woman experiences. The only available scientific method is the alkaline haematin method.[9]This is precise enough for

intensive clinical trials but has always been considered to be clinically impractical. Test samples of blood, either as liquid or soaked into sanitary napkins, vaginal tampons, or cotton pads are incubated at room temperature in 5% (w/v) aqueous sodium hydroxide solution. After incubation, absorbance of the brown-colored alkaline haematin is measured at 550 nm in a spectrophotometer against a blank of either 5% sodium hydroxide or distilled water. The quantity of blood in each sample, represented by eluted, haematin-converted hemoglobin, is determined from a standard curve relating various known volumes of incubated blood to absorbance at 550 nm (A550). Standard volumes of blood are always incubated for the same length of time as the samples. When the samples are diluted with more sodium hydroxide solution than the standards, sample absorbances are multiplied by an appropriate dilution factor. The photometric alkaline haematin procedure indicates a sensitivity to less than 0.1 ml of blood, and an accuracy of measuring human menstrual blood from most sanitary devices generally within plus or minus 5%. The method appears to be specific for menstrual blood and independent of other materials in genital fluids. Menstrual discharge could be stored for at least 1 month prior to determination without alteration of results. maximum normal menstrual blood flow is between 60 and 80 ml, and the mean is near 30 ml. Variation of measured flow between consecutive menstrual cycles in some individuals (both normal and menorrhagic) reveals the necessity for repeated measurements to properly assess average blood flow in certain cases. [10]

Other simpler pictorial methods are available, which give a score for the amount of blood per sanitary pad, the nights with soiling, staining of clothes, and the total number of pads. But this method have not been adopted worldwide.[11]

The majority of women have no experience of the quantity of other women's menstrual loss so they cannot make even a semi quantitative assessment with any reliability. The actual diagnosis of heavy menstrual loss is

usually based on the patient's history as interpreted by the gynecologist rather than any formal method of menstrual assessment.[12][1]

The patient who presents with such bleeding presents two distinct but important challenges for the clinician. The first is the exclusion of cancer or hyperplasia; the second is dealing with the annoyance as well as the fear that the bleeding engenders in the patient. Any attempt at appropriate therapy, whether surgical, hormonal or expectant, begins with an accurate diagnosis. Transvaginal ultrasound with saline infusion sonohysterography for selective patients has emerged as a safe, non-invasive, and inexpensive method of triaging patients with abnormal uterine bleeding in order to determine which patients require no further evaluation, blind endometrial sampling for a global endometrial process or visually directed endometrial sampling when pathology is thought to be focal.[13]

Specific investigations for a suspected cause of menorrhagia should be performed according to the clinical finding and clinical evaluation.[13]

1-2-5 Bleeding disorders and menorrhagia:

As it has been mentioned, menorrhagia is a common problem among women of reproductive age. It is often a problem for women with inherited bleeding disorders.[6]

The United States US Centers for Disease Control and Prevention (CDC) program for women with bleeding disorders has included a series of collaborative research projects with the goals of establishing the prevalence of bleeding disorders; assessing physician awareness; improving diagnostic testing techniques; and evaluating treatment and management options. To better understand the population of women with bleeding disorders, CDC began by surveying 75 women with the most common bleeding disorder, von Willebrand disease (vWd), who were receiving care in hemophilia treatment centers (HTCs) across the United States. This internal survey addressed the origin of referral to

the HTC, symptoms experienced before diagnosis, diagnostic processes, services provided and perceptions of the HTC care. Four findings were of particular interest: 86% of the women reported a long history of excessively heavy menstrual bleeding (menorrhagia), which was by far the most common symptom; it took an average of 16 years from the onset of symptoms until the woman learned she had vWd; more than half of the women had to be tested many times before receiving a diagnosis; and a large proportion of these women underwent surgical procedures, including hysterectomy, to alleviate the discomfort and effects of menorrhagia. In the survey, physicians were given a list of conditions, which included vWd, and were asked to rank each condition as a likely, uncertain or unlikely cause of menorrhagia. Only 3% of the responding physicians would consider vWd as a likely cause of menorrhagia in a woman aged 15 to 44. When asked the question "Given 1,000 women with menorrhagia, in your opinion, how many would be due to an inherited bleeding disorder," the answer, on average, was less than 1%. Although in practice an average of 20 years, 42% of the responding physicians reported never having seen a woman with menorrhagia who had a bleeding disorder. Furthermore, the survey showed that gynecologists virtually never refer a woman with unexplained menorrhagia to another specialist.[14] Reports from Sweden and England indicated a higher prevalence of vWd and other bleeding disorders in women with menorrhagia (17% to 37%)[15,16] than perceived by the physicians in this survey. As a next step in the research agenda, CDC again collaborated with Emory University to perform an epidemiological study to determine the prevalence of bleeding disorders in a population of American women with menorrhagia in order to corroborate or refute the European findings. The study was conducted with women enrolled in a health maintenance organization during a specified time period. Participants were either of two groups: women with a diagnosis of menorrhagia according to the medical record or were among a random sample of women without the diagnosis who had seen a gynecologist

for other reasons. About half of the women in the study were African American. Laboratory testing performed at CDC showed that 8.2% of the women with menorrhagia had vWd or another clotting factor deficiency compared to 0.8% of the women without menorrhagia. To mimic the European studies, the diagnosis of vWd was examined separately for Caucasian and African American women. Significantly, vWd was found in 15.9% of white women with menorrhagia and in only 1.4% of African American women with menorrhagia. Two conclusions could be drawn from the findings of this study:

First, the data supported the European studies indicating that the prevalence of vWd and other bleeding disorders in Caucasian women (about 15%) was greater than the less than 1% perceived by gynecologists, and second, the prevalence of vWd may vary by race.[5]

With sufficient epidemiological evidence of a high prevalence of bleeding disorders among women with menorrhagia, gynecologists face the dilemma of deciding which women should be tested for a bleeding disorder. Though, for the patient, coagulation testing entails only drawing a blood sample, the laboratory analysis is nevertheless expensive and must be performed by a laboratory experienced in coagulation. Along with the issue of who should be screened for bleeding disorders is a controversial list of how to screen. The CDC prevalence study revealed racial differences in vWd. With this discovery, CDC laboratory scientists examined coagulation factors in Caucasians and African Americans without bleeding disorders or other health problems. This research found baseline racial differences in several haemostatic parameters, specifically higher von Willebrand factor and factor VIII in African Americans compared to Caucasians.[6,17] Furthermore, preliminary data indicate that platelet disorders are more prevalent in African American women than in Caucasian women.[18] CDC is exploring the diagnostic and clinical implications of these racial differences. Another question in testing for vWd is whether to consider the menstrual cycle in determining when to test. Von Willebrand factor levels are

affected by estrogen. Underdiagnosis of vWd could result if raised estrogen levels, which occur at certain times during the menstrual cycle, give a falsely high reading of von Willebrand factor, thus causing a false negative test for vWd. Until recently, the consensus among hematologists has been to ignore the menstrual cycle when testing for vWd. However, recent data from CDC indicate that the lowest von Willebrand factor levels are on days one to four of the cycle (during menses) suggesting that this is the best time to test.[19] Laboratory research into new and better diagnostic procedures and techniques for women with bleeding disorders is ongoing at CDC and elsewhere. Until these new tests are developed, CDC encourages individuals who suspect a bleeding disorder to seek testing from laboratories experienced in coagulation in order to prevent the need for multiple tests to achieve an accurate diagnosis.

The CDC research team on women with bleeding disorders recommends screening for vWd in adolescents with severe menorrhagia, adults with unexplained significant menorrhagia and before hysterectomy indicated for excessive menstrual bleeding.[20][21]

The CDC undertook another survey of all obstetric/gynaecology in Georgia to ascertain the prevalence of menorrhagia among their patients and to determine the physicians' perceptions of bleeding disorders as a potential cause. Based on a 54 percent response rate, the survey indicated that about 8 percent of these physicians' patients experienced menorrhagia, but physicians rated bleeding disorders as the least likely cause for this problem. Indeed 42 percent of the responding physicians reported that they had never seen a patient with menorrhagia due to a bleeding disorder. This evidence clearly indicates a widespread lack of awareness of bleeding disorders in women among the obstetric/gynaecology providers.[21]

1-2-6 Women and Bleeding Disorders:

There are several types of bleeding disorders that affect women. von Willebrand disease (vWd) is the most common inherited bleeding disorder and may affect up to 2.5 million American women. Women may also be "symptomatic carriers" of hemophilia, meaning that in addition to carrying the gene, they also exhibit symptoms similar to mild hemophilia. All of the rare factor deficiencies, which include factor I, II, V, VII, X, XI and XIII, can also result in bleeding among men and women. Platelets disorders and vascular abnormalities are also recognized causes of bleeding. Aside from the fact that women have similar symptoms to men with bleeding disorders, they can also experience added obstetric and gynecological complications. vWd and other bleeding disorders are particularly troublesome for reproductive-aged women. Heavy and prolonged menstrual bleeding, can lead to serious complications if left untreated. Other common symptoms include recurrent nosebleeds, easy bruising, bleeding from the digestive or urinary tract and excessive bleeding from the mouth or gums.

Some doctors may not be familiar with bleeding disorders affecting women, making a definitive diagnosis elusive. It is common for bleeding symptoms to be attributed to other causes or to simply go unexplained. The troubling aspect to this problem is that non-surgical treatments are available for these conditions. In cases where a woman with a bleeding disorder (or symptomatic carrier) becomes pregnant, she should see an obstetrician as soon as possible. This will ensure that the doctor can consult with the local hemophilia treatment center to provide pre- and postnatal care for the woman and her baby. Decisions about what medical and surgical options to pursue should be based on personal preference, family planning goals and severity of bleeding problems.[22]

1-2-7 Pathophysiology of bleeding disorders:

The haemostatic system consists of platelets, coagulation factors, and the endothelial cells lining the blood vessels as well as the vessel wall. The body's reaction to vessel wall injury is rapid adhesion of platelet to subendothelium. The initial haemostatic plug, composed primarily of platelets, is stabilized further by a fibrin mesh generated in secondary haemostasis. The arrest of bleeding in a superficial wound, such as the bleeding time wound, almost exclusively results from the primary haemostatic plug. Platelet disorders lead to defects in primary haemostasis and have signs and symptoms different from coagulation factor deficiencies (disorders of secondary haemostasis).[23]

1-2-7-1 Primary haemostasis:

The platelets arise from the cytoplasmic fragmentation of megakaryocytes in the bone marrow and circulate in blood as disk-shaped anucleate particles.

Under normal circumstances, the resistance of the endothelial cell lining to interactions with platelets and coagulation factors prevents thrombosis. When endothelial continuity is disrupted and the underlying matrix is exposed, a coordinated series of events are set in motion to seal the defect (primary hemostasis). Platelets play a primary role in this process, interacting with subendothelium-bound von Willebrand factor (vWf) via the membrane glycoprotein Ib complex. This initial interaction (platelet adhesion) sets the stage for other adhesive reactions that allow the platelets to interact with each other to form an aggregate .

The platelet glycoprotein (glycoprotein IIb/IIIa) complex mediates platelet-to-platelet interactions (platelet aggregation). On resting platelets, glycoprotein IIb/IIIa is unable to bind fibrinogen or vWf. Platelet activation allows binding of these proteins, which bridges adjacent platelets. Morphologically, the platelets change dramatically from disks to spiny spheres in a process called shape change.

Platelets contain two unique types of granules, the alpha granules and the dense granules. The alpha granules contain haemostatic proteins such as fibrinogen, vWf, and growth factors (e.g., platelet-derived growth factor). The dense granules contain proaggregatory factors such as adenosine 5'-diphosphate (ADP), calcium, and 5-hydroxytryptamine (serotonin). During activation, the granules are centralized and their contents are discharged into the lumen of the open canalicular system, from which they are then released to the exterior (the release reaction).

Following activation, platelets have 2 major mechanisms to recruit additional platelets to the growing haemostatic plug. They release proaggregatory materials (e.g., ADP) by the release reaction, and they synthesize thromboxane A2 from arachidonic acid. Thus, the release reaction and prostaglandin synthesis act to consolidate the initial haemostatic plug by promoting the participation of other platelets in the growing haemostatic plug. In addition, when platelets are activated, negatively charged phospholipids move from the inner to the outer leaflet of the membrane bilayer. This negative surface provides binding sites for enzymes and cofactors of the coagulation system, resulting in the formation of a clot (secondary haemostasis).[23,24]

1-2-7-2 Stabilization of the platelet plug by fibrin (secondary haemostasis):

Definitive haemostasis is achieved when fibrin formed by blood coagulation is added to the platelet mass and by platelet induced clot retraction/compaction.

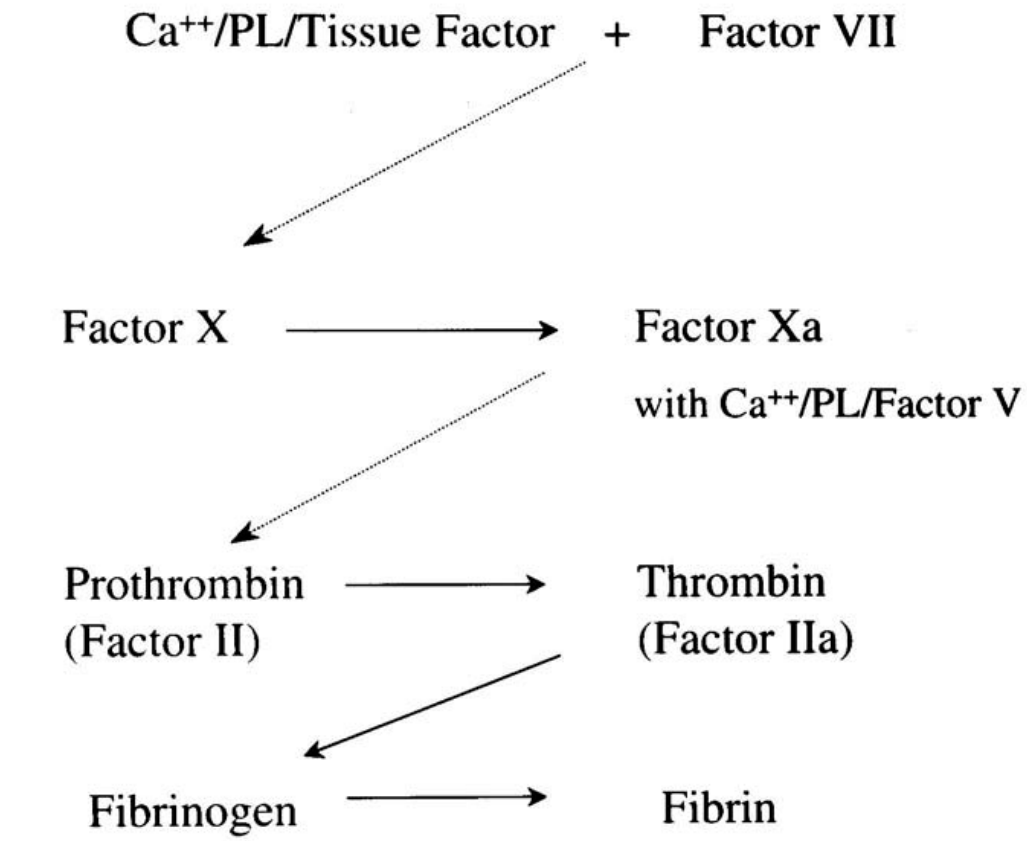
Following vascular injury, the formation of excessive Xase (VIIa, TF, PL and Ca^{2+}), and known as extrinsic pathway (fig1-1), is necessary and sufficient to initiates the coagulation cascade in vivo. Thrombin generated at the injury site converts soluble plasma fibrinogen into fibrin, potentiates platelet aggregation and secretion and also activates factor XI and XIII and cofactor V and VIII. The contact system (Intrinsic Pathway fig1-2) therefore does not appear to have a

physiological role in haemostasis.[24] Platelet aggregation and release reactions accelerate the coagulation process by providing abundant membrane phospholipid. The fibrin component of the haemostatic plug increases as the fused platelets autolyse and after few hours the entire haemostatic plug is transformed into solid mass of cross linked fibrin, factor XIII is responsible of crosslinking and stabilization of fibrin. In the final phase of normal hemostasis, fibrinolysis, the fibrin clot undergoes an orderly process of degradation. Deficiencies in the normal inhibitors of fibrinolysis, such as alpha 2-antiplasmin or plasminogen activator inhibitor-1, may be underdiagnosed causes of delayed bleeding because they are not identified by the usual coagulation screening tests.[23,24]

Primary haemostatic disorders are characterized by prolonged bleeding time, and the characteristic physical examination findings are petechiae and purpura. In comparison, defects in secondary haemostasis exhibit delayed deep bleeding (e.g., muscles and joints) and the characteristic physical examination finding is Haemarthrosis. Haemarthrosis and muscle hematomas are not present in primary haemostatic disorders.[24]

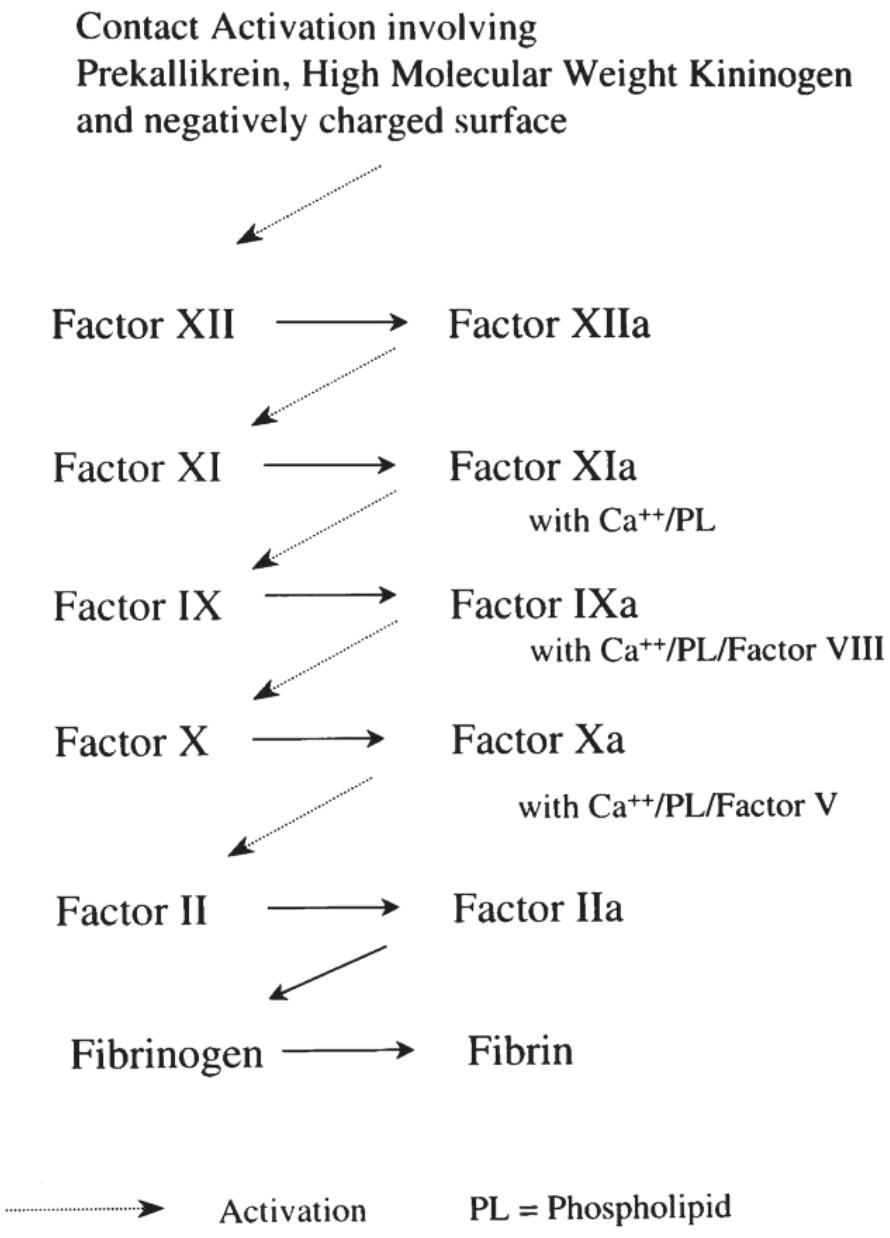
Disorders of primary hemostasis, including thrombocytopenia and von Willebrand disease, are particularly important to consider when evaluating women with abnormal uterine bleeding. Patients with acquired or congenital deficiencies of either coagulation factors or the regulators of the fibrinolytic system may also present with menorrhagia. Accurate diagnosis of a bleeding disorder is essential to the design of an appropriate therapeutic regimen and is likely to have important clinical implications beyond that of the presenting gynecologic complaint.[23]

Fig(1-1):Extrinsic pathway:



PL = Phospholipid ⋯⋯→ Activation

Fig(1-2) Intrinsic pathway:



1-2-8 Disorders of haemostasis:

1-2-8-1 Hereditary coagulation factors disorders :

1-2-8-1-1 Von Willebrand's disease:

von Willebrand's disease is the most common inherited bleeding disorder. It is autosomal dominant, and its prevalence is estimated to be as high as 1 case per 1000 individuals.

The hallmark of von Willebrand's disease is defective platelet adhesion to subendothelial components caused by a deficiency of the plasma protein vWf. This factor is a large, multimeric protein synthesized, processed, and stored in the Weibel-Palade bodies of the endothelial cells, and it is secreted constitutively following stimulation. VWf has a major role in primary hemostasis as mediator of the initial shear-stress–induced interaction of the platelet to the subendothelium via the glycoprotein Ib complex. In addition, von Willebrand protein acts as a carrier and stabilizer of coagulation factor VIII by forming a complex in the circulation. In the absence of vWf, the factor VIII level is low. In classic hemophilia A, the factor VIII level is low because of a deficiency of factor VIII itself, whereas in von Willebrand disease, the factor VIII level is low because of a deficiency in its carrier protein. [24,25]

von Willebrand disease is a relatively mild bleeding disorder, except in the occasional patient who is homozygous for the defect and who has severe bleeding often indistinguishable from classic hemophilia. The bleeding manifestations are predominantly skin-related and mucocutaneous (i.e., easy bruising, epistaxis, GI hemorrhage). Most bleeding episodes occur following trauma or surgery. In women, menorrhagia is common, often exacerbated by the concurrent administration of cyclooxygenase inhibitors. Pregnant patients with this disease usually do not have problems.

Bleeding time is prolonged in persons with von Willebrand disease. Because the von Willebrand protein is phase reactant (i.e., increased synthesis in the presence of inflammation, infection, tissue injury, and pregnancy), a mild prolonged bleeding time may be normalized, resulting in difficulty in diagnosis.

In addition to the prolonged bleeding time, characteristic abnormalities in platelet aggregation tests occur. In patients with von Willebrand disease, platelets aggregate normally to all agonists except ristocetin. The antibiotic ristocetin induces binding of the von Willebrand protein to platelets, similar to what happens with platelets following vessel wall injury in vivo. Ristocetin-induced platelet aggregation correlates with the platelet-aggregating activity of the von Willebrand protein. Levels of coagulation factor VIII are also low, resulting from a decrease in vWf. [24,25]

Variants of von Willebrand disease:

Von Willebrand disease results from either a quantitative or qualitative defect in von Willebrand factor (vWf), a large multimeric protein which mediates platelet adhesion and serves as a carrier protein for factor VIII.

There are three main types of von Willebrand disease. Type 1 is characterized by a partial deficiency of vWf antigen. It accounts for 70-80% of cases and is usually mild. Type 2 is caused by abnormalities in the von Willebrand protein leading to functional defect of the vWf protein. It consists of four subtypes based on their different pathophysiologic mechanisms (table 1-1). A common variant (type IIA) results from functionally defective vWf that is unable to form multimers. Larger multimers are more active in mediating platelet vessel-wall interaction. In these variants, the factor VIII level may be normal. In the type IIB variant, the von Willebrand protein has heightened interaction with platelets, even in the absence of stimulation. Platelets internalize these multimers, leading to a deficiency of von Willebrand protein in the plasma. Both types 1 and 2 are transmitted as an autosomal dominant trait. Type 3 is

characterized by a virtual absence of von Willebrand factor and is, therefore, typically severe. It is an autosomal recessive disorder and affected individuals are either homozygotes or compound heterozygotes.[23]

A disorder of platelet glycoprotein Ib has also been described. In this condition, increased affinity for von Willebrand protein in the resting stage leads to the depletion of plasma von Willebrand protein. This disease is called pseudo von Willebrand disease or platelet-type von Willebrand disease. [23,24]

Table(1-1) Subtypes of type 2 vWD: [24]

Subtype	Platelet aggregation	Factor VIII binding capacity	High MW vWf multimers
2A	Decreased	Normal	Abscent
2B	Increased affinity for GPIb	Normal	Usually reduced/ abscent
2M	Decreased	Normal	Normal or ultra large
2N	Normal	Reduced	Normal

1-2-8-1-2 Haemophilia A and B:

Haemophilias A and B result from deficiencies of coagulation factors VIII (FVIII) and IX (FIX), respectively. They are less common than von Willebrand disease but are the most common severe inherited bleeding disorders. They can cause significant morbidity and mortality through a spectrum of bleeding manifestations of various severities, for example, easy bruising, deep muscle and joint haemorrhage, spontaneous or post-surgery/post-traumatic bleeding and intracranial bleeding. Both are X-linked recessive disorders: men inherit the

condition and women are affected as carriers. Haemophilia A affects 1 in 5 000 , live male births and haemophilia B 1 in 30 000 live male births. Carriers of haemophilia usually have a clotting factor level around 50% of normal as they have only one affected chromosome. However, a wide range of values (22-116 iu/dl) have been reported as a result of lyonisation (random inactivation of one of each pair of X chromosomes). Some haemophilia carriers have very low factor levels and are, therefore, at risk of severe bleeding complications.[23,26]

Carrier detection for haemophilia is based on four different methods:

- Pedigree analysis, using the knowledge of X-linked recessive inheritance, to assess a woman's risk from her position in the family tree. Daughters of a man with haemophilia are obligate carriers.
- Phenotypic assessment based on assays of plasma FVIII, FIX and, in some cases, vWf.
- Direct gene mutation detection.
- Indirect gene analysis involving the use of linked polymorphic markers to track heredity of a haemophilia gene within a pedigree when the mutation is not known.

Direct gene analysis allows definitive diagnosis of carrier or non-carrier status while the other methods only ascertain risk of carriership of haemophilia. As 20% of all people with haemophilia A and 50% of those with severe haemophilia have intron 22 inversion mutation, this is the starting point of direct mutation detection for severe cases. Mutation screening is performed in the remaining 80%. When this not possible, linkage analysis is then undertaken.[23]

Preconceptual counseling: has two roles. The first is to provide women and their partners with adequate information on the genetic implications of their disorders, their reproductive choices and the management of their pregnancies, including options of prenatal diagnosis. This will assist them to reach a decision that is appropriate to their situation. Psychological support should be available during all aspects of counseling with an understanding of the ethnic and cultural

influences on each individual. The second is to allow planning for pregnancy and to perform a trial of desmopressin if appropriate. Other aspects of preconceptual care include immunization against hepatitis A and B for those likely to require blood transfusion and general advice, for example, regarding folic acid supplementation. [23]

Table(1-2):**Clinical and laboratory findings in haemophilia A,B and vWd:[24]**

	Haemophilia A	Haemophilia B	vWd
Inheritance	Sex linked	Sex-linked	dominant(incomplete)
Main site of haemorrhage	Muscle, joint, post trauma or postoperative	Muscle, joint, post trauma or postoperative	Mucous membranes, skin cuts, post-trauma or postoperative
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Prothrombin time	Normal	Normal	Normal
Partial thromboplastin time	Prolonged	Prolonged	Prolonged or normal
FactorVIII	Low	Normal	May be moderately reduced
FactorIX	Normal	Low	Normal
VWF	Normal	Normal	Low or abnormal function
Ristocetin-induced platelet aggregation	Normal	Normal	Impaired

1-2-8-1-3 Hereditary disorders of other coagulation factors:

All these disorders (deficiency of fibrinogen, prothrombin, factor V,VII, combined V and VIII, factors X,XI, XIII) are rare. In most the inheritance is autosomal recessive. They are much rarer than the haemophilias, they are expressed clinically only in homozygotes or compound heterozygotes. The underlying molecular defects and actual management of bleeding episodes are not well established as for haemophilia A and B.

In countries where consanguineous marriages are frequent such as the Muslim world, recessively inherited coagulation deficiencies are more frequent and together reach prevalence higher than haemophilia B, representing a significant clinical and social problem. Their relative frequencies in the Islamic republic of Iran when compared with those registered in UK and Italy, are found to be three to seven times more frequent in Iran, except factor XI deficiency, because it is prevalent among Ashkenazi Jews, who are not common in that community. [24]

Autosomal recessively inherited coagulation deficiencies are generally less severe than haemophilias. The only exceptions are factor X and XIII deficiencies, characterized by the early onset of life threatening symptoms such as umbilical cord and central nervous system bleeding. Among the other disorders , a minority have spontaneous haemarthrosis and muscle haematomas. Mild bleeding symptoms such as epistaxis is very frequent among them. In afibrinogenaemia and factor V deficiency, this mucosal type bleeding may be explained by a concomitant defect of the protein in the patients' platelets reflected by prolonged bleeding time, however no obvious explanation for the frequency of epistaxis and menorrhagia in defects of other factors such as prothrombin, factor VII and X. No evidence they cause reduced fertility or recurrent miscarriages, with the exception of factor XIII deficiency. Haematuria is also rare symptom except for factor X deficiency.[24]

1-2-8-2 Acquired coagulation disorders: [24]

The acquired coagulation disorders are more common than the inherited disorders. Unlike the inherited disorders, multiple clotting factor deficiencies are usual.[23,24] they can occur in association with multisystem disease or pharmacological intervention. They may also occur at the extremes of age and in association with pregnancy.

Below is a list of some of the causes of acquired coagulopathy:

Deficiency of vitamin K-dependant factors:

This can occur in a variety of conditions, e g, Biliary obstruction, malabsorption of vitamin K (e g. tropical sprue, gluten induced enteropathy),vitamin K antagonist therapy(e.g. coumarins, indandiones), antibiotic therapy and haemorrhagic disease of the newborn.

Liver disease:

Can cause deficiency of vitamin K dependant factors and other factors synthesized by the liver.

Disseminated intravascular coagulation:

Consumptive coagulopathy, low platelets count, and fibrin degradation products which interfere with coagulation and platelet function.

Inhibition of coagulation

Specific inhibitors (e.g. antibodies against factor VIII)

Non specific inhibitors(e.g. antibodies found in anti phospholipid syndrome, systemic lupus erythematosus SLE, rheumatoid arthritis…etc.)

Miscellaneous

Therapy with heparin, defibrinating agents or thrombolytics

Massive transfusion syndrome and cardio pulmonary bypass surgery.

Alcoholism

Diseases with M-protein production

L-asparaginase

Hypothermia

1-2-8-3 Disorders of platelet :

Platelet defects can be considered either as a decreased number of platelets (thrombocytopenia) or as defective platelets. Platelet aggregation tests are useful in differentiating various disorders of platelet function.

1-2-8-3-1Thrombocytopenia:

It is a platelet count less than the reference range of normal (150-400x10^9/l). Spurious thrombocytopenia can occur due to aggregates forming in the specimen. Also, dillutional thrombocytopenia may occur in situations of fluid replacement or blood component replacement without platelet support. In all cases of thrombocytopenia, the peripheral blood smear must be reviewed to confirm the thrombocytopenia. This review is crucial.

Thrombocytopenia can be further divided into increased destruction or decreased production. Thrombocytopenia resulting from increased destruction occurs either by an immune mechanism(e g, autoimmune, alloimmune, drug-induced), or increased consumption. Platelets are consumed intravascularly by the activation of the coagulation process (diffuse intravascular coagulation DIC) or by deposition on damaged endothelial cells (microangiopathy).

Production defects result from those diseases that cause bone marrow failure, such as aplastic anemia, isolated megakaryocytic aplasia, infiltration by leukemia or other malignancy, fibrosis or granulomatous disorders or tuberculosis; and other congenital and hereditary condition of thrombocytopenia.

Functional disorders of platelets are relatively rare, and most of these disorders are mild and may not be recognized early in life. They can be inherited (rare) or acquired (common).[25]

1-2-8-3-2Disorders of platelet function:

Disorders of platelet function are as follows:

Disorders of platelet adhesion (Bernard-Soulier syndrome)

Disorders of aggregation (Glanzmann thrombasthenia)

Disorders of secretion

Disorders of thromboxane synthesis

Acquired disorders of platelet function (drugs, eg, aspirin, NSAIDs, alcohol)

Uremia

Paraproteins

Fibrin degradation products

Myelodysplasia or a myeloproliferative syndrome.[24,25]

1-2-8-3-2-1 Bernard-Soulier syndrome:

This syndrome results from a deficiency of platelet glycoprotein protein Ib, which mediates the initial interaction of platelets to the subendothelial components via the von Willebrand protein. It is a rare but severe bleeding disorder. Platelets do not aggregate to ristocetin. The platelet count is low, but, characteristically, the platelets are large, often the size of red blood cells, and may be missed because most automatic counters do not count them as platelets. [25]

1-2-8-3-2-2 Glanzmann thrombasthenia:

This results from a deficiency of the glycoprotein IIb/IIIa complex. Platelets do not aggregate to any agents except ristocetin. Both Bernard-Soulier syndrome and Glanzmann thrombasthenia are characterized by life-long bleeding. Although platelet transfusions are effective, they should be used only

for severe bleeding and emergencies because alloantibodies often develop in these patients. [25]

1-2-8-3-2-3 Disorders of secretion and thromboxane synthesis:

During primary hemostasis, thromboxane synthesis and released ADP play a major role. A mild bleeding diathesis ensues if these mechanisms are deficient. Thromboxane synthesis disorders are almost always caused by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs).

Mutations in the enzyme that converts arachidonic acid to thromboxane A2 have been described and are associated with a life-long bleeding diathesis. Similarly, an absent or defective receptor for thromboxane A2 also leads to an aspirin like aggregation defect. In disorders of release reaction, platelets fail to secrete proaggregatory ADP following activation. The defects result from either the absence of granules in platelets or the defective storage of ADP. ADP is present in the dense granules of platelets as a storage pool, which is not used in the normal metabolic activity of platelets (in contrast to the metabolic pool).

Disorders of secretion and thromboxane synthesis are mild platelet disorders and often respond to desmopressin (DDAVP) infusion, which seems to improve haemostatic function. If severe bleeding is present, these disorders can also be managed effectively with platelet transfusions. Cryoprecipitate has also been reported to be very effective.[24,25]

1-2-8-3-2-4 Platelet dysfunction in uremia:

Abnormal bleeding is common in patients with uremia. The bleeding has the characteristics of a platelet disorder, and GI tract bleeding is the most frequent symptom. Bleeding time is generally very prolonged in patients with uremia, signifying a major defect in platelet function, which improves after dialysis. A number of dialyzable platelet-inhibitory factors have been shown to inhibit platelet function. Furthermore, uremic platelets synthesize less

thromboxane A2, and the blood vessels taken from patients with uremia produce greater quantities of platelet-inhibitory prostaglandin. Nitric oxide produced by the endothelial cells inhibits platelet function. Because the prolonged bleeding time and the haemostatic abnormalities are partly corrected by red blood cell transfusion or erythropoietin therapy, the failure of hemoglobin to quench excess nitric oxide synthesis has been suggested as partly responsible for the platelet dysfunction. [25]

1-2-8-4 Vascular disorders:

The rare vascular disorders are a heterogeneous group of conditions characterized by easy bruising and spontaneous bleeding from small vessels. The underlying abnormality is either in the vessels themselves or in the perivascular connective tissues.

Most cases of bleeding caused by vascular defects alone are not severe. Frequently, the bleeding is mainly in the skin causing petechiae, ecchymoses or both. In some disorders there is also bleeding from mucous membranes. In these conditions the standard screening tests are normal. The bleeding time is normal and other tests of haemostasis are also normal. Vascular defects may be inherited or acquired.[24]

1-2-9 Tests of haemostatic function: [24]

A number of simple tests are employed to assess the platelet and coagulation components of haemostasis.

- Blood count and blood film examination.
- Screening tests of blood coagulation.(table1-3)
- Specific assays of coagulation factors.
- Bleeding time.
- Tests of platelet function.
- Test of fibrinolysis.

Table(1-3) **Screening tests used in the diagnosis of coagulation disorders: [24]**

Screening test	**Abnormality indicated by prolongation**	**Most common cause of disorder**
Thrombin time(TT)	Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin or FDPs	DIC , Heparin therapy
Prothrombin time(PT)	Deficiency or inhibition of one or more of the following coagulation factors: VII, X, V, II, Fibrinogen.	Liver disease Warfarin therapy DIC
Activated partial thromboplastin time(APTT)	Deficiency or inhibition of one or more of the following coagulation factors:XII, XI, IX, VIII, X, V, II, Fibrinogen.	Haemophilia, Christmas disease,(+conditions above)
Fibrinogen quantitation	Fibrinogen deficiency	DIC Liver disease

1-2-10 Management of menorrhagia in women with inherited bleeding disorders:

A multidisciplinary approach is required for diagnosis and treatment. Gynaecological supervision is always required to exclude organic causes unmasked by the bleeding disorder. Treatment options are similar to those for menorrhagia in general with the addition of desmopressin and replacement therapy and the exclusion of non-steroidal anti-inflammatory drugs. The therapeutic plan should take into consideration the patient's preferences, age and severity of bleeding. Iron supplementation is of paramount importance. Remedies used in clinical practice for menorrhagia in general (tranexamic acid, combined oral contraceptives [COC], levonorgestrel intrauterine system [LNG-IUS]) are first tried. In case of failure or contraindication (COC and LNG-IUS are best avoided in adolescents), before considering surgical options, treatment with desmopressin becomes the preferred choice in patients known to be responsive. The availability of desmopressin preparations for self-administration makes home treatment feasible in well selected cases. The treatment is efficacious and safe provided that patients are instructed to self-administer the agent only during the first two or three more heavy days of menstrual period, for a maximum of three to four doses and no more than two consecutive administrations at a 12-h interval.[27,28] plasma or factor replacement may be needed in some cases.

1-3 Justifications

Menorrhagia is a very annoying problem. It can seriously affects women's quality of life in different ways, for example; many women limit the amount of time they work or change careers as a result of bleeding problems, many women are unable to work normally during their menstrual periods, many women have lost faith in the medical profession after being told for years their problems were not real, they might suffer constant fatigue from iron deficiency anemia, some women suffer from depression as a result of the stress of their bleeding disorder, many women suffer pain during their menstrual periods and times of ovulation, many girls and women must live with the embarrassment of staining due to heavy bleeding. Adolescents in particular would face the psychological trauma of the frightening sight of excessive bleeding, which could be their first experience with menstruation. Many women have had hysterectomies, their bleeding symptoms were ignored and doctors could not diagnose their bleeding disorder, this means they could not have any more children[15].

Menorrhagia is a common complaint in the gynaecology departments as observed by many doctors in practice, yet there is no objective informations about how frequent is it in Sudan. Many patients may not show an obvious cause, gynaecologist may suffer searching for the aetiology of such a disorder, many times symptomatic and blind treatment is offered to them. Many patients with known bleeding disorder, suffer from excessive menstruation.[3]

Considering haemostatic abnormalities as a possible cause of menorrhagia, this study was carried out to assess the prevalence of bleeding disorders among females presenting with menorrhagia in Khartoum hospital. This is the first study to deal with this issue in Sudan.

1 -4 Objectives:

1-4-1 Major objectives:

- To assess the prevalence of bleeding disorders among women presenting with menorrhagia.
- Classification of the types of bleeding disorders among the study population.

1-4-2 Minor objectives:

- To measure the bleeding time, prothrombin time and activated partial thromboplastin time of the study population.
- To do other factors assay when coagulation abnormality is suspected.
- To screen for factor XIII deficiency when other screening tests are normal.
- To do platelet count and finger prick platelet aggregation.
- To measure the level of von willebrand's factor antigen and factor VIII assay for all the study population.

Chapter Two

2. METHODOLOGY

2-1- Study design:

This is a cross-sectional descriptive study from December 2007 to February 2008.

2-1-2- Study area:

The study was conducted in the Obstetrics and Gynaecology Referred Clinic (Fath Alrahman Albashir), and haemophilia unit, Khartoum Teaching Hospital.

2-1-3- Study population:

Females in the reproductive age presenting to Khartoum Teaching Hospital, complaining of menorrhagia. Which was confirmed by a gynaecologist.

2-1-3-1 Inclusion criteria:

Any female in the reproductive age, with gynaecologist diagnosis of menorrhagia, and normal ultrasonography and hormonal assay.

2-1-3-2 Exclusion criteria:

With exclusion of:

- known cases of bleeding disorders.
- gynecological malignancy or fibroid.
- use of intra uterine device.
- liver disease and renal disease.

- Use of anticoagulants within the last 2months.
- use of nonsteroidal anti inflammatory agents, e g Aspirin and anti platelets drugs within 14 days of participation.

2-1-4 Ethical consideration:

A verbal consent was taken after being informed by all details of the objectives of the study, and its health emphasis in the future.

2-2 Data collection:

2-2-1 Pre coded questionnaire (appendix 1):

A questionnaire was specifically designed to obtain informations about the demographic data of the study population, as well as bleeding history and family history.

Some of the data was obtained from records of patients investigated within the haemophilia unit, who presented with menorrhagia as a chief complaint, and had no previous diagnosis of bleeding disorder.

2-2-2 Investigations:

Preliminary screening was done: bleeding time, prothrombin time and partial thromboplastin time; as well as platelet count and finger prick platelet aggregation. when any coagulation abnormality was found, further tests and appropriate factor assay was performed. Von Willebrand antigen and factor VIII level were done for all patients. Factor XIII assay was done when no other abnormality was found.

2-2-2-1 Equipment:

1. Syringes.
2. Containers with anti coagulant: EDTA and Tri Sodium Citrate.
3. Lancets.
4. Filter paper.
5. Alcohol swabs and cotton gauze.
6. Centrifuge capable of generating at least 1700 g.
7. Temperature-controlled waterbath maintaining temperatures of 37°C ± 1°C.
8. Stopwatches.
9. Automatic adjustable pipettes in the range of (0 -200 µl) and up to 1000 µl.
10. Calibrated pipette for delivery of liquid volumes up to 5 ml.
11. Test tubes.
12. Glass slides.
13. Coagulometer (BIOPASS):

***Principle of action*:**

It acts by mechanical detection based on ball method. It measures the time from addition of the starter reagent to the onset of in vitro clot formation. The sample is located in the cuvette inclined at an angle, which is slowly turned about its longitudinal axis. A surface treated steel ball is located at the bottom of the cuvette by means of gravity. The time measurement starts with the addition of the starter reagent. At the onset of coagulation the fibrin clot pulls the ball along. The positional change of the ball triggers an impulse in a magnetic sensor which electronically stops the timer.

14. Other additional equipment is required for some procedures including: A microtitre plate reader for enzyme-linked immunosorbent techniques (ELISA).

2-2-2-2 Materials:

Reagents used will be mentioned with each method.

2-2-2-3 samples collection and preparation:

After cleaning with alcohol swab, five milliliters of venous blood were collected from the antecubital fossa of sitting patients-using a disposable 5 mls syringe. 2.25 mls was drawn immediately into a container containing 0.25 mls of 13.3g/l aqueous tri sodium citrate (9 parts of freshly collected blood to one part of tri sodium citrate). The other 2.5 mls were delivered into a container with EDTA (Ethylenediamine tetra acetic acid) anticoagulant. Both containers were then mixed well and gently and taken to the laboratory for analysis within two hours.

EDTA sample was used for platelet count measurement; citrated sample for preparation of platelet poor plasma (ppp). A platelet poor plasma was obtained by centrifugation at 2500g for 15 minutes. Then used for coagulation testing; PT, aPTT and TT (when needed). The rest of (PPP) was frozen at -20^0c for further testing; VWf ag, factor XIII screening, and specific factor assay if indicated.

2-2-3 Methods of estimation:

2-2-3-1 Bleeding time: (Duke Method)

The ear lobe was cleaned and warmed, a sharp sterile lancet was used to make a prick in the earlobe, timer was stated as soon as the first drop of blood appeared. Filter paper was used to plot the drop of blood every 15 seconds. The bleeding time was recorded when the bleeding stopped. Normal range (<7min)[29].

2-2-3-2 Finger prick platelet aggregation:

This is a simple procedure to assess the ability of the platelet to form an aggregate.

Procedure:

The middle finger was cleaned and dried. Using a lancet, the finger was pricked. A drop of blood was placed on three slides 30 seconds apart; blood smear was made; stained by Leishmain stain and examined under the microscope.

Platelet aggregates were expected to be found in the second and third slide indicating normal platelet function.

2-2-3-3 Platelet count:

The EDTA anticoagulated blood sample (above) was used for platelet count determination. Sysmex automated hematology analyzer KX-21N was used. reference range ($150 \times 10^9/l - 400 \times 10^9/l$) [29].

2-2-3-4 Prothrombin time PT(appendix 2):

Sample:

platelet poor plasma (ppp).

Principle:

This test reflects the overall efficiency of the extrinsic system. It is sensitive to changes in factor V, VII and X, and less so to factor II (prothrombin). It is also unsuitable for detecting minor changes in fibrinogen level, but may be abnormal if the fibrinogen level is very low or if there is an inhibitor present. The sensitivity of the test is influenced by the reagent and technique used and it is important to establish a reference range locally.

Equipment:

- Stopwatch.
- Pipettes.

- Water bath.
- Coagulometer: its principle of action is mentioned earlier.

Reagents:

Thromboplastin (which contains calcium chloride), purchased from DiaMed AG (appendix)

procedure:

1. After switching on the coagulometer, the cuvettes were placed in the unheated preparation area. pre warming of the reagent was done.
2. The steel peads were dispensed into the cuvettes.
3. 0.1 ml of the commercial control plasma and patient plasma were pipetted , each one in a separate cuvette. Then they were placed in the rotating test area and incubated at 37c for 3 minutes.
4. Then timer was started by adding the 0.2 ml of PT reagent.
5. The results were recorded in seconds. **(**Each test was done in dublicate).
6. Reference range was taken as 11-14.[30]

2-2-3-5 Activated partial thromboplastin time (APTT)(appendix 3):

Principle:

This is a non-specific test of the intrinsic system. Taken together with a normal prothrombin time, it is the most useful screening test for detecting deficiencies of factors VIII, IX, XI and XII.

The APTT will also be prolonged in any deficiency involving the common pathways (deficiencies of factors V, X, II and to a lesser extent fibrinogen) and in the presence of inhibitors. The presence of some therapeutic inhibitors of coagulation, such as heparin, will also prolong APTT. It is important to rule out these treatments as a cause of prolonged APTTs before continuing with other tests.

Equipments:

- Pipettes.
- Stopwatches.
- Coagulometer.

Reagents:

- APTT reagent (purchased from DiaMed AG (appendix).

Procedure:

1. The cuvettes were placed in the unheated preparation area. pre warming of the reagent was done.
2. The steel peads were dispensed into the cuvettes.
3. 0.1 ml of the commercial control plasma and patient plasma were pipette, each one in a separate cuvette. Then they were placed in the rotating test area.
4. 0.1 ml of the PTT reagent was added and incubated at 37°C. After 3 minutes, 0.1 ml of calcium chloride was added and the timer started.
5. The reading of the coagulometer was recorded in seconds.
6. Reference range was taken as (23-33)seconds.

2-2-3-6 Thrombin clotting time (TT):

Principle:

The thrombin time reflects the reaction between thrombin and fibrinogen.

Thrombin

Fibrinogen Fibrin

It is prolonged when the fibrinogen level is very low, in the presence of heparin and heparin-like substances, in the presence of other inhibitors, e.g. fibrin(ogen) degradation products (FDPs) and

when fibrinogen is qualitatively1 abnormal (dysfibrinogenaemia).

Equipment:

• Test tubes

• Stopwatches

• Pipettes

• waterbath

Reagents (DiaMed):

• Thrombin solution which induces clotting of normal plasma in about 15 seconds

• Control plasma

Method:

1. 0.2 ml test and control plasma were Pipetted into separate cuvettes.

2. Warmed to 37^0 C.

3. 0.2 ml thrombin added to each tube. Timer started and clotting time was recorded for each tube.

referance range: (15-19 seconds)[29]

4. Test was done in duplicate.

Results/Interpretation

The thrombin reagent used gave a clotting time of around 15 seconds with control normal plasma.

2-2-3-7 Further investigation of abnormal PT and APTT:

Principle:

Plasma samples found to have abnormal screening tests, i.e. PT/APTT, were further investigated to determine the cause of the abnormality. Knowing the principle that abnormal PT or PTT will be corrected ,if mixed (50:50) with normal plasma, by more than 50% of the difference between the clotting times of the normal and test plasma, and hence factor deficiency is indicated. And when

the test plasma is mixed (50:50) with plasma of known coagulation factor deficiency, the level of the deficient factor is then determined.

2-2-3-7-1 Factor assay:(Appendix 4)

A reduction of single factor activity can be determined by carrying out a one stage test (thromboplastin time PT, or partial thromboplastin time PTT) with known factor deficient plasmas. The principle of this test rests on the fact that, all the other factors necessary for coagulation are present in sufficient quantities in the deficient plasma. The factor deficiency can be quantified as a percentage by using a calibration curve.

Reagents:

1. Factor deficient plasma.
2. Owren's Veronal Buffer, PH 7.35.
3. PT or PTT reagens.

Procedure:

Following the procedure mentioned in the KIT (appendix); fresh normal plasma (PPP) was used to set a calibration curve. Double dilution starting with 1/10 (as the 100% activity) was made; PT or PTT was done for each dilution ; and reading plotted on a double log paper.

The test plasma was treated the same; after mixing with deficient plasma. the reading of 1/10 dilution was taken from the curve as the value of the factor activity of the test plasma.

*NB!: Poor correction of the 50:50 mix of test plasma with normal plasma, suggests an inhibitor, possibly to one of the clotting factors in the system or of the non-specific type, such as lupus anticoagulant.

When they are suspected, inhibitors of specific coagulation factor may not appear at zero time, and correction of the initial mix should not be interpreted until the incubation time is completed.

2-2-3-9 factor XIII screen:

Principle

Thrombin and calcium (Ca^{2+}) are required to activate FXIII so that it will crosslink fibrin into a stable form. In this method, despite using citrated plasma, sufficient Ca^{2+} ions are still available for XIII activation. A normal ethylene diamine tetracetic acid (EDTA) anticoagulated plasma is used for a control. In this plasma, EDTA chelates the calcium ions completely, which means that the factor XIII is not able to crosslink fibrin. Addition of 2% acetic acid or 5 M urea results in the lysis of non-crosslinked clots. Citrated plasma with greater than 10 u/dl of FXIII activity has an insoluble clot.

Equipments:

- 75 × 10 mm glass tubes.
- Stoppers

Reagents:

- 0.9% saline.
- 30 u/ml thrombin.
- Normal EDTA plasma.
- Urea.

Method:

1. 0.2 ml citrated test plasma was added to 0.2 ml 0.9% saline in glass tube. Repeated with 0.2 ml EDTA normal plasma, for a negative control, and repeated with 0.2 ml normal citrated plasma, for a positive control.
2. To each tube 0.1 ml of 30 u/ml thrombin was added and mixed.
3. Then the tubes were Left for 30 minutes at 37°C.
4. Flicking the tubes to loosen clot from side of tube.
5. 5 ml of 5 M urea was added to each tube and stopperd. then tubes were left at room temperature overnight.

Results/Interpretation:

EDTA plasma should have no visible clot.

Normal citrated plasma should have an intact clot visible.

If a clot is not visible in the test plasma, the subject has factor XIII deficiency.

Normal range:

Normal subjects have visible clot after overnight incubation.

2-2-3-10 Von Willebrand antigen assay:((Appendix5)

Antigenic assay for the quantitative determination of von Willebrand factor by the enzyme linked immunosorbent assay (ELISA).

Principle:

The vWf to be measured by specific rabbit anti-human vWf antibodies coated on the internal walls of a plastic microplate well. Next, rabbit anti-vWf antibodies coupled with peroxidase bind to the remaining free antigenic determinants of vWf. The bound enzyme peroxidase is revealed by its action on the on the tetramethyl benzidine (TMB) substrate.

After stopping the reaction with strong acid the intensity of the color is directly proportional to the concentration of vWf initially present in the sample.

Samples:

platelet poor plasma which was stored at -20^{0}c. Assayed as a patch analysis.

reagents and equipments:

A kit provided by asserachrom vWF: Ag.(appendix)

In addition to:

- 1 M sulfuric acid.

- Plate reader set at 450 nm.
- Common laboratory equipments and materials (centrifuge, vortex , stop watch, pipettes, distilled water..)

procedure:

All the steps prescribed by the kit provider (appendix) was followed.

The results were interpreted from the plotted curve mentioned in the test procedure.

2-4 Data analysis:

Data analyzed using Microsoft excel program (2007) for windows vista, and SPSS 11.01 computer program .

Chapter Three

3. Results

This descriptive study was conducted in Khartoum territory, in the period (Dec2007-Feb2008).Data was collected from patients who presented with menorrhagia, after being evaluated by a gynaecologist to exclude a gynaecological cause. Part of the data was taken from records of haemophilia unit in Khartoum, for patients investigated for menorrhagia as a presenting complaint. No previous diagnosis of bleeding disorder was known.

- Thirty four women who fulfill the inclusion criteria were examined and investigated to assess their bleeding profile. Their ages ranged between 13 and 43 with a mean age of 25 years old, fig(3-1). Their distribution according to age groups, showed > 70% were less than 30 years old. The highest frequency38% fell within (21-30) age group.
- eleven women(32.5%) out of 34 women with menorrhagia, complained of other bleeding symptoms , mainly epistaxis. table(3-1)
- Positive family history of bleeding symptoms was found in nine menorrhagia patients (26.6%) .table(3-2)
- 19 women (56%) were found to have haemostatic abnormality (table3-3) . these were; platelet disorders (47%), vWd(32%), factor X deficiency(10.5%) and factor V deficiency (10.5%). table(3-4)
- Table (3- 5): shows menorrhagia patients with other symptoms of bleeding in relation to the diagnosis of bleeding disorder. It has a P value of 0.004*, which is highly significant.

- Table (3-6) correlates the diagnosis of bleeding disorder to positive family history of bleeding. P value of 0.447, which is statistically not significant.

When analyzing the laboratory data:

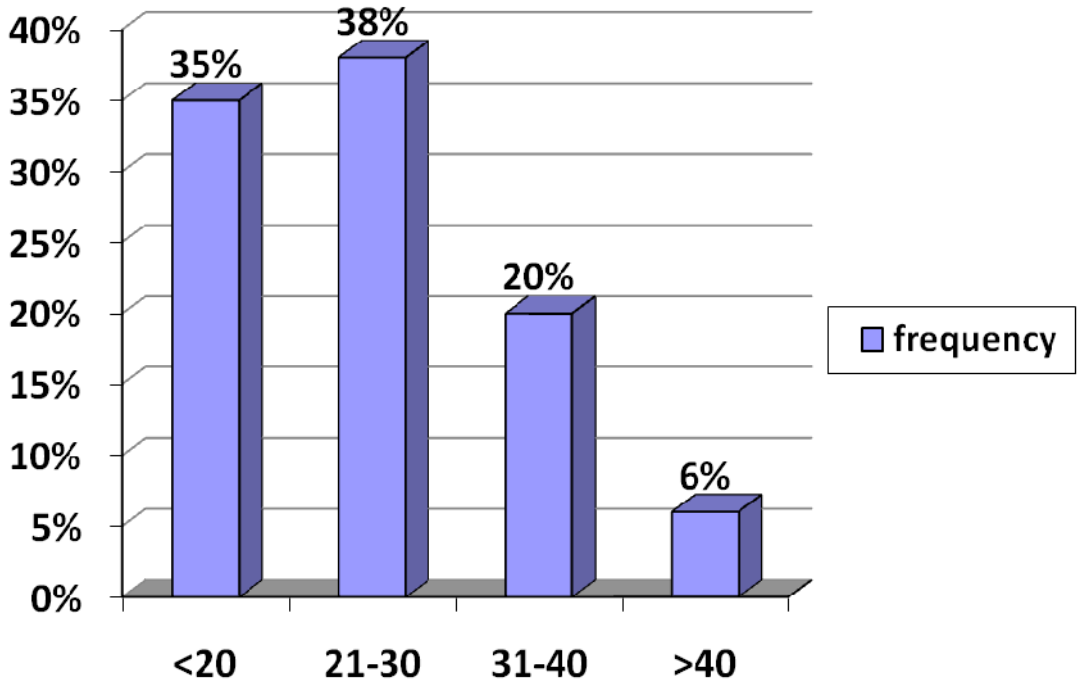
- Basic screening was abnormal in 21 (62%) of the study population. when further evaluated; almost 90% of those who screened abnormal were found to have bleeding disorder; while 73% of those who test negative were found to be normal. These findings gave a p value of 0.000 which is highly significant. And sensitivity and specifity of the screening tests of 89.5% and 73.3% respectively(table3-7).
- Prolonged bleeding time >7miutes was seen in eight patients, seven of them with platelet abnormality and one with VWD. Table (3-8)and(3-9)
- Table (3-10) and table(3-11): showed platelet count distribution and finger prick platelet aggregation, respectively. low platelet count was found in 7 patients (ref. range 150-400x10^9/l), 3 of them with defective aggregation. Two patients had very low platelet count, rendered their aggregation difficult to be assessed.
- Prothrombin time with reference range of (11-14) seconds, was prolonged in 12 women; seven of them with mild prolongation having the value of 15-17 seconds. Five patient with significantly prolonged PT: two of them have factor V deficiency, two with factor X deficiency, and one with borderline level of factor VII (55%). Table(3-12)
- Activated Partial Thromboplastin Time ref. range (23-33 seconds) was abnormal in nine women of the study population, four of them were vWd, two with factor X deficiency and two with factor

V deficiency, one woman showed a borderline level of vWf. table(3-13)

- All values of prolonged PT or PTT were corrected by 50:50 mix with normal plasma. Further assessment was made using appropriate deficient plasma.
- Thrombin Time (TT), done when both PT and PTT were prolonged, showed normal values (ref range 15-19 seconds)[29]
- Factor VIII level and vWf:ag levels were shown in table (3-14)and table(3-15) respectively. Their ref. range (50-150%). Two patients have low level of factor VIII <50%, both of them have low vWf:ag level. On the other hand, 6 out of 34 patients (17.6%), have low level of vWf:ag and other two with borderline level.
- Table (3-16) demonstrates the laboratory findings in the six menorrhagia patients with a diagnosis of von Willebrand Disease.
- Factor XIII screening was normal for all the studied patients.

* Statistical analysis and cross tabulation using x^2test. With level of significance of p value < 0.05

Fig(3-1): **Age distribution of the study population:**



The total number is 34 women.

Table(3-1):Symptoms of bleeding among the study population:

Symptoms	Frequency	Percent
Menorrhagia alone	23	67.6%
Menorrhagia + other symptom of bleeding	11	32.4%
Total	34	100%

Table(3-2): Family history of bleeding among patients with menorrhagia.

Family history of bleeding	Frequency	Percent
Yes	9	26.5%
No	25	73.5%
Total	34	100%

Table (3-3): The frequency of bleeding disorders among the study population:

	Frequency	Percentage
Bleeding disorder	19	56%
Normal	15	44%
Total	34	100%

Table(3-4): Types of bleeding disorder among women with menorrhagia:

Bleeding disorder	Frequency	(Percent%)
Platelet disorders	9	(47%)
VWD	6	(32%)
Factor V deficiency	2	(10.5%)
Factor X deficiency	2	(10.5%)
Total	19	(100%)

Table (3-5) : Presence of other Bleeding symptoms within patients in relation to the diagnosis of bleeding disorder:

	No bleeding disorder	bleeding disorder	Total
menorrhagia alone	14	9	23 (67.6%)
menorrhagia +other symptoms	1	10	11 (32.4%)
Total	15 (44%)	19 (56%)	34 (100%)

P value: 0.004

Table (3-6):Family history of bleeding in relation to the diagnosis of bleeding disorder:

		Bleeding disorder		Total
		Yes	No	
Family history of bleeding	Positive	6	3	9
	Negative	13	12	25
Total		19	15	34

P value : 0.447

Table (3-7): Screening tests of haemostasis of the study population.

		Screening test		Total
		Abnormal	Normal	
Bleeding disorder	Yes	17	2	19 56%
	No	4	11	15 44%
Total		21 62%	13 38%	34 100%

P value: 0.000

Sensitivity: 89.5%

Specifity: 73.3%

Table(3-8): Bleeding time within the study population(ref. range2-7) [29]:

Bleeding time in minutes	≥ 7 minutes	<7 minutes	Total
Frequency	8 (24%)	25 (76%)	33 (100%)

Table(3-9) Bleeding time and diagnosis of bleeding disorders.

		Bleeding time in minutes		Total
		< 7	≥ 7	
Bleeding disorder	No	14	0	14 42%
	Yes	11	8	19 58%
Total		25 76%	8 24%	34 100%

P value : 0.005

Table(3-10): Platelet count groups.

Platelet count $x10^9/l$	Frequency	Percent
<150	7	20.6%
150-400	24	70.6%
>400	3	8.8%
Total	34	100%

Table (3-11):Finger prick platelet aggregation.

Platelet aggregation	Frequency	Percent
Positive	28	87.5%
Negative	4	12.5%
Total	32	100%

Table (3-12): Prothrombin time (PT) in seconds (ref. range 11-14) :

PT in seconds	Frequency	Percent
11-14	22	65%
15-17	7	20%
>17	5	15%
Total	34	100%

Table (3-13): Activated Partial Thromboplastin Time APTT in seconds (ref. range 23-33):

APTT in seconds	Frequency	Percent
23-33	25	73%
34-40	4	12%
>40	5	15%
Total	34	100%

Figure (3-14): Factor VIII level % in the study population, ref. range (50-150%):

Factor VIII level%	Frequency	Percent
<50	2	6%
50-100	26	76.5%
101-150	6	17.5%
Total	34	100%

Table (3-15): VWf:ag level % within the study population. Ref. range(50-150%):

vWf:ag level %	Frequency	Percent
<50	6	17.5%
50-100	21	62%
101-150	7	20.5%
Total	34	100

Table(3-16): Findings in patients with vWd:

Patient No.	Age Years	Bleeding Time(min)	aPTT (control 28-30 sec.)	vWf:ag level %	Factor VIII level%	Family history
1	20	4	39	42	52	No
2	43	3	36	42	65	No
3	13	3	26	24	65	No
4	23	4	37	22	44	No
5	13	4	32	8	85	No
6	20	14	56	1	11	Yes

Chapter Four

Discussion

Menorrhagia is a common gynaecological symptom, a specific cause is identified in less than 50% of affected women, it may be a manifestation of an underlying inherited disorder of coagulation. Kadir etal[15] found that: 73% of women with Von Willebrand Disease, 57% of women who are carriers of Hemophilia A or B and 59% of women with Factor XI Deficiency suffer from menorrhagia.

This study was designed to assess the prevalence of bleeding disorders among women presenting with menorrhagia in Khartoum hospital.

Thirty four women in the reproductive age, were included In this study. They had a diagnosis of menorrhagia , with no gynaecological cause identified. Their ages ranged between 13- 43 years old; most of them were adolescents and young adults.

When they were investigated for haemostatic abnormality; nineteen of them (56%) were found to have bleeding disorders; including platelet disorders(47%); vWd (32%); coagulation factors deficiencies; factor X 10.5%and factor V 10.5%.

A similar study was done in Gorgia ; forty seven percent of women with menorrhagia were found to have bleeding disorders.[21] Mitchel L. Zoler, reported in a study of 30 patients at one institution in Philadelphia, that about half of adolescents with menorrhagia have an underlying bleeding disorder.[31] Another study done by Kadir RA etal, revealed a frequency of bleeding disorders of 17% of which13% were vWd and 4% Factor XI deficiency, platelet disorders were not fully evaluated[15]. 120 women from western India aged between 18 and

35 years presenting with menorrhagia without any obvious cause were studied for bleeding disorders. 19.16% (23 cases) had an inherited coagulation disorder. The majority (11.6%) were patients with von Willebrand's disease (vWD), rare platelet disorders such as Glanzmann's thrombasthenia (3.3%), Bernard-Soulier syndrome (0.83%), coagulation factor deficiencies such as factor VIII (0.83%), factor X (0.83%), and factor XI (0.83%), and immune thrombocytopenia (0.83%) were also found.[32]

Data from another Indian study reported that , there were 337 women having inherited bleeding disorder from 2200 women with menorrhagia. Platelet abnormalities were the most prevalent disorders,86%; followed by vWd,11.9%.[33]

There is evidently a wide variation in the prevalence of bleeding disorders among patients presenting with menorrhagia within different studied groups. This in part can be explained by different designs used to study these abnormalities or due to difference in methods used for their investigation. Noteworthy that, the epidemiology of bleeding disorders itself is widely variable. Some studies found a substantial difference in vWd prevalence among white and black Americans , as well as platelet abnormalities; they found that for unknown reason, African American women have higher levels of vWf and factor VIII. Platelet disorders is more common in black American.[14,15,18] Other rare autosomal recessive hereditary coagulation disorders exhibit similar variation, they are found to be relatively more common in Muslim countries and parts of India and middle east, this was due to the increased frequency of consanguineous marriages within these communities. Moreover, some hereditary disorders were shown to be clustered within specific groups e.g. factor XI deficiency in Ashkenazi Jews[24].

No similar studies were done in our country or even a comparable group of people, so we cannot assess the compatibility of these findings.

A history of bleeding symptoms other than menorrhagia, mainly epistaxis, was a significant finding in this study. It might be used as a predictor of presence

of bleeding disorder. This finding is supported by the west Indian study[32], which reported that; history of bleeding from other sites howsoever minor, paternal consanguinity as well as family history of bleeding tendencies appeared as a very strong predictor for such kinds of disease in patients with menorrhagia.[32]

Nine women of the study population had family history of bleeding, six of them were found to have bleeding disorder while the remaining three showed no haemostatic abnormality, these 6 patients demonstrates one third of patients with bleeding disorders. On the other hand about half the patients with no family history of bleeding had abnormal haemostasis. These findings were proved not to be significant statistically (table3-6), hence they can support the possibility of bleeding disorder but cannot be used as a predictor of their presence. In contradistinction to what mentioned in the west Indian study[32], and to another study by Yasmin, which found that The only statistically significant predictor was a family history of bruising and bleeding among teenagers presenting with menorrhagia[34] . Family history specially for excessive menstrual bleeding is difficult to assess. Often, women themselves did not realize they were not normal. Their bleeding problem ran in the family. Therefore sisters, mothers, grandmothers, and aunts often had the same problem. Nobody saw it as special or, if they did, they said, "All the women in our family bleed a lot during their periods.[14,16]

The pattern of inheritance of bleeding disorders is also variable, that most of the hereditary disorders are autosomal recessive, and even the autosomal dominant ,like vWd, has different penetrance[24,35].

Most of the patients with inherited coagulation defects were adolescent and young adults, indicating their severity. All the four patient with factor V and X deficiency reported presence of other symptoms of bleeding, and their menorrhagia commenced with menarche. The later finding was not available for all the study population, hence its significance was not assessed. Patients with

mild symptoms do not present early to seek medical advice, nevertheless, bleeding disorders themselves have very variable clinical presentation, patients might suffer no, or very minor symptoms and only bleed during major challenge like surgery or child birth.[35]

Screening tests used in this study were found to be more sensitive than specific, this is consistent with what mentioned in the literature.[29,35]Although its sensitivity could have been better if more evaluation was done for the positive findings. For example patients with prolonged aPTT and borderline levels of vWf could have lower levels of vWf if the test was repeated in different occasion.

Of the 33 women tested for their bleeding time; eight women had prolonged bleeding time and all of them had a bleeding disorder (p value 0.005). Seven of them had platelet disorder and only one with vWd. Bleeding time is controversial as a screening test, it has no predictable pattern; it is best viewed as being sensitive but not specific[35]. There are different methods for its determination, standardization of these test procedures is not easily feasible. Recently, platelet function analyser PFA-100, is getting acceptance as a preferred method to determine bleeding time. The PFA-100 measures the time it takes for a specimen of citrated whole blood in a capillary tube to block a membrane by forming a platelet plug, a parameter known as the closure time. Closure time is a measure of platelet aggregation and adhesion.[31]A recent study in Philadelphia; which included 30 girls aged 11-16 years (mean age was 13); who were referred for assessment following a clinical diagnosis of menorrhagia; stated that; it was a good way to assess bleeding disorders in these young patients with a platelet function analyzer, such as the PFA-100, Dr. Victoria J. Davis said during the annual meeting of the North American Society for Pediatric and Adolescent Gynecology:"I would use this test instead of bleeding time measurements to screen patients for a bleeding disorder. We are confident that two sequential, positive results using the platelet function analyser identify patients who have a platelet-function or clotting disorder," she concluded[31].

Table(3-10) demonstrated that platelet count was low in seven patients, two of them showed abnormal aggregation by finger prick method, they might have Bernard Soulier disorder if evaluated further. Three patients with mild elevation of platelet count, with values less than $600x10^9/l$, could have for example iron deficiency which is common finding in such patients, or they might have ongoing bleeding.

Finger prick platelet aggregation was defective in four patients, this is a crude simple test which is unable to define the exact abnormality of platelet function..

PT (table3-12) the reference range was 11-14 seconds according to the kit used, PT was mildly prolonged in 7 patients having the value of 15 seconds, these were not regarded as significant abnormalities and no further investigations were performed. PT was significantly prolonged >17 seconds in five women ; two of them with factor V deficiency, two with factor X deficiency, with very prolonged PT, and one with borderline factor VII level (55%). Factor VII deficiency is associated with severe bleeding including a high frequency of intracranial haemorrhage. Oddly, some patients with very low levels do not manifest bleeding, and even thrombosis has been reported[35]. This patient with isolated prolongation of PT and significant bleeding history and family history, needs further evaluation.

PT is an easy test with end point easy to be determined and clear cut results. Standardization of its result can be achieved by using International Normalization Ratio (INR) rather than measured values.[29,35]

Using a normal range for APTT (23 -33)seconds, table(3-13), it was found to be abnormal in nine menorrhagia patients; four of them had low levels of vWf, two with factor X and two with factor V deficiencies. another woman with mildly prolonged APTT had borderline vWf levels, the possibility of vWd variants cannot be excluded, since no functional assay was performed. Still type I vWd could be suspected, because in this study the time of sampling was not

related to specific time in the menstrual cycle . vWf is an acute phase reactant, its level is affected by estrogen and many other factors which can cause higher levels leading to difficulty in diagnosing vWd[19]. The severity of bleeding was not assessed, as it is not included in the design of this study.

Most of the patients had factor VIII and vWf:ag levels between 50-100%.tables (3-14, 3-15). This necessitates the establishment of local reference ranges. For proper interpretation of results.

Table (3-16) which demonstrates the laboratory findings in the six women with vWd, shows a prolonged bleeding time in only one patient. it is known that the bleeding time could be prolonged or normal in vWd, still the procedure used in this study has an inherent error, may be different results would have been obtained if another sensitive method was used.

Another finding is the normal or mildly prolonged aPTT in vWd patients which is not an uncommon finding , adding to the difficulties in diagnosing vWd, which can be easily missed by routine screening tests.[19]Most patients were adolescents and young adults, only one old lady was diagnosed, adding to what mentioned earlier about delayed diagnosis of many patients with bleeding disorders.[15] VWf:ag was almost absent as well as factor VIII which was markedly reduced in only one patient, who could be classified as type 3 vWd. This was the only patient with vWd who had very prolonged bleeding time and positive family history of bleeding, indicating severe disease. Another patient with low vWf:ag (8%), strangely had normal factor VIII level 85%, which needs more evaluation. The rest of vWd patients seemed to be type 1 which is the commonest type. All of these vWd patients had normal platelet count excluding vWd variants associated with abnormal platelet count. Two patients with borderline vWf:ag level, one of them had mildly prolonged aPTT the other had a normal aPTT. They were discussed earlier.

Difficulties faced in this study:

- No previous data about menorrhagia and bleeding disorders in Sudan to build on it , and to assist in the design of this study.

- The study population were cooperative during the initial interview. But when tried to contact them for more sampling for confirmation of the initial findings, they were reluctant.

- The samples had to be processed within short time in a laboratory distant from the collection site, hence very few samples to be taken per day.

- The reliability of inclusion of individuals was not assessed by the study design, it depended on a gynaecologist evaluation, who might face the difficulties of the definition of menorrhagia itself and the assessment of the amount of bleeding.

- The requirements for performing all the laboratory testing were not available in a single place.

- No local reference ranges available for proper interpretation of laboratory results.

Chapter Five

Conclusions and recommendations

Conclusions

- Haemostatic abnormalities were found to be prevalent among patients presented with menorrhagia in this study.

- Platelet abnormalities were the most common bleeding disorders causing menorrhagia among the study population; followed by vWd.

- Other rare coagulation factors deficiencies , can also manifest as menorrhagia. They were found to be prevalent among the study population.

- Simple screening tests, although somewhat sensitive, still can miss some cases of bleeding disorders. Especially vWd which can evade diagnosis by routine testing.

- Still the design of this study did not cover all aspects of haemostasis, e.g. fibrinolysis, so their presence cannot be excluded

- Presence of other symptoms of bleeding might be used as a predictor of the presence of bleeding disorder.

- Family history of bleeding was not a predictor of the presence of bleeding disorders as a cause of menorrhagia. However it might support its presence

Recommendations

- Haemostatic disorders should be suspected whenever there is significant bleeding symptoms in patients with menorrhagia without an obvious cause. They should be investigated within a reliable laboratory, for proper management and before performing any invasive procedure.
- Specialized, reliable laboratory should be available, to limit the variability of test results , and to perform further testing when screening tests are abnormal.
- vWd should have special consideration in patients with menorrhagia , since it can be missed by routine testing.
- A bigger well controlled study should be performed to find out the actual prevalence of bleeding disorders in the general population in Sudan as well as among patients with gynaecological bleeding including menorrhagia.
- There should be a joint clinic or referral system, for collaborate evaluation of gynaecological bleeding and menorrhagia in particular, and for sharing opinion between haematologists and gynaecologists, so as to alleviate the suffering of patients, wondering without a diagnosis for a long time.

References

1. Elund, Mans. Aspects on Menstrual Physiology, Pathology and Medical Treatment of Menorrhagia. nov28,2003. Dissertation from Karolinska Institute. http://diss.kib.ki.se/2003/91-7349-669-3/

2. CG. Heavy menstrual bleeding: Understanding NICE guidance , National Institute for Health and Clinical Excellence (UK) (24 January 2007) . http:// Wikipedia. the free encyclopedia /Menorrhagia. last modified on 6 June 2009

3. Dilly A, Drews C, Miller C, etal. Von Willebrand's disease and other inherited bleeding disorders in women with diagnosed menorrhagia. 2001. Obst Gynecol;97:630-6.

4. Claire S. Philipp, Ambarina Faiz, etal. Age and Prevelance of Bleeding Disorders in Women With Menorrhagia. 2005. Obstetrics and Gynecology;105:61-66.

5. Killick SR and Maguiness SD. Department of Obstetrics and Gynaecology, University of Hull, Medical Forum introduction, UK 1997. Last modified: 15-06-2007.

6. NIH, DHHS. Women with Bleeding Disorders. June 2, 2004. NHLBI Working Group Report. Last updated: November 8, 2004.

7. Julia A shaw, howard A Shaw. Menorrhagia. http://emedicine.medscape.com/obstetrics gynecology, Medical editor Thomas Michael Price, Updated: Jan 12, 2007.

8. Sally Crudder, R.N., **Women and Bleeding Disorders:** A Misdiagnosed and Underreported Women's Health Issue. Introduction to Bleeding Disorders and Epidemiological Perspective. January 14,1999. Hemophilia Treatment Center

Program, H Centers for Disease Control and Prevention Brown Bag Seminar Series.

9. Hallberg L, Nilsson L, Determination of menstrual blood loss. 1964. Scand J Clin Lab Invest; 16: 244-8.

10. Shaw ST, Aaronson DE, Moyer DL, Quantitation of menstrual blood loss--further evaluation of the alkaline hematin method. 1972 Jun. Contraception,;5(6):497-513.

11. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. 1990. Br J Obstet Gynaecol; 97: 734-9.

12. Hallberg L, Hogdahl AM, Nilsson L, etal. Menstrual blood loss - a population study. 1966. Acta Obstet Gynaecol Scand; 45: 320-51.

13. Goldstein SR. Menorrhagia and abnormal bleeding before the menopause. 2007. Obstetrics and Gynecology.

14. Dilley A, Drews C, Lally C, et al. A survey of gynecologists concerning menorrhagia: perceptions of bleeding disorders as a possible cause. 2002. Journal of Women's Health and Gender-Based Medicine; 11 (1):39-44.

15. Kadir RA, Economides DL, Sabinb C, et al. Frequency of inherited bleeding disorders in women with menorrhagia. 1998. Lancet:351:485- 89.

16. Ediund M, Blomback M, von Schoultz B, et al. On the value of menorrhagia as a predictor for coagulation disorders. 1996. American Journal of Hematology;53:234-38.

17. Dilley A, Drews C, Miller C, et al. von Willebrand disease and other inherited bleeding disorders in women with diagnosed menorrhagia. 2001. Obstetrics and Gynecology,97:630-36.

18. Miller C, Dilley A, Richardson L, et al. Population differences in von Willebrand factor levels affect the diagnosis of von Willebrand disease in African-American women. 2001. American Journal of Hematology; 67:125- 29.

19. Miller C, Dilley A, Drews C, Richardson L, et al. Changes in von Willebrand factor and factor VIII levels during the menstrual cycle. 2002. Thrombosis and Haemostasis:87:1082-83.

20. ACOG Committee Opinion No. 263. Von Willebrand's Disease in Gynecological Practice. 2001. Obstetrics/Gynecology: 98(6); 1185-86.

21. Anne Dilley, Bleeding Disorders in Women. January/February2003. HEMAWARE vol8, issue 1.

22. http://www.hemophilia.org/NHFWeb/MainPgs/MainNHF, bleeding.last updated (2/3/2009).

23. Ewenstein BM. The pathophysiology of bleeding disorders presenting as abnormal uterine bleeding. 2001 Apr. Obstetric /Gynecol.;97(4):630-6.

24. Hoffbrand A.V, Daniel Catovsky, Edward G.D. Tuddenham. Postgraduate Haematology, fifth edition 2004. Blackwell publishing Ltd.

25. Perumal Thiagarajan. Platelet Disorders. http://www.emedicine.com/specialties.htm. Last Updated: July 20, 2006.

26. Claudia Chi, and Rezan A Kadir. Management of women with inherited bleeding disorders in pregnancy. 2007. The Obstetrician & Gynaecologist;9:1:27-33

27. Rodeghiero F. Management of menorrhagia in women with inherited bleeding disorders: general principles and use of desmopressin. 2006 Feb. Obstet Gynecol .;61(2):136-45.

28. Stewart A, Cummins C, Gold L, etal."The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review." Jan 2001. BJOG 108 (1): 74-86.

29. S M Lewis, B J Bain, I Bates. Dacie and Lewis Practical Haematology. Ninth edition 2001.p12. Chirchill Livingstone.

30. Steve Kitchen, Angus McCraw. Diagnosis of Haemophilia and Other Bleeding Disorders, a Laboratory manual.1992. The World Federation of Haemophilia.

31. Mitchel L. Zoler. Underlying bleeding disorders implicated in half of all menorrhagia cases in adolescents - Platelet Function Test. July 1, 2003. OB/GYN News.

32. Sucheta A. Trasi, Anil V. Pathare, Shrimati D. Shetty, etal. The spectrum of bleeding disorders in women with menorrhagia: a report from Western India. 2005. Annals of Hematology, Volume 84, Number 5, 339-342

33. R. Saxena, M. Gupta, R. Kashyap, etal. Inherited bleeding disorders in Indian women with menorrhagia. March 2003. Haemophilia 9 (2),193-196.

34. JAYASINGHE Yasmin; MOORE Patricia1; DONATH Susan; etal. Bleeding disorders in teenagers presenting with menorrhagia. October 2005 . Australian and New Zealand Journal of Obstetrics and Gynaecology, Volume 45, Number 5, pp. 439-443(5).

35. Vademecum. Hemostasis and Thrombosis.first edition 1999. © Landes Bioscience.

Appendix 1

Questionnaire

Number ☐☐ contact no……

Name: ……

Age:☐☐

tribe:……..

residence:……

marital status:…… single : ☐ married: ☐

Menarche:…… ☐

Katamena:…… ☐

Duration of menorrhagia: …… ☐☐

History of bleeding from other sites: yes ☐ No ☐

Drug history:

NSAID within 2 weeks:……yes ☐ No ☐

Hormonal therapy:……yes ☐ No ☐

Family history of bleeding:……yes ☐ No ☐

……

Investigations:

1. Bleeding time:…….
2. Platelet count:……
3. Finger prick platelet aggregation:…….
4. PT:…….
5. aPTT:……
6. F VIII level:…….
7. VWF level:…….
8. F XIII assay:……..
9. Other factors:……